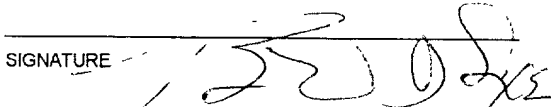


533 Rec'd PCT/PTO 20 JUL 2000

FORM PTO-1390 (Modified) (REV 5-93)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER <b>040283/0182</b>	
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				U.S. APPLICATION NO. (known, see 37 CFR 1.55) <b>09/600631</b> UNASSIGNED	
INTERNATIONAL APPLICATION NO. <b>PCT/GB99/00223</b>		INTERNATIONAL FILING DATE <b>22 January 1999</b>		PRIORITY DATE CLAIMED <b>23 January 1998</b>	
TITLE OF INVENTION <b>AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS</b>					
APPLICANT(S) FOR DO/EO/US <b>David Reginald ADAMS, Jon BENTLEY, Corinna Dagmar BODKIN, Ian Anthony CLIFFE, James Edward Paul DAVIDSON, Howard Langham MANSELL, Nathaniel Julius MONCK and Joy Miriam SHEPHERD, heiress of Robin Gerald SHEPHERD (deceased)</b>					
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:					
1.	<input checked="" type="checkbox"/>	This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.			
2.	<input type="checkbox"/>	This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.			
3.	<input type="checkbox"/>	This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).			
4.	<input checked="" type="checkbox"/>	A proper Demand for International Preliminary Examination was made by the 19 <sup>th</sup> month from the earliest claimed priority date.			
5.	<input checked="" type="checkbox"/>	A copy of the International Application as filed (35 U.S.C. 371(c)(2))			
	<input type="checkbox"/>	is transmitted herewith (required only if not transmitted by the International Bureau).			
	<input checked="" type="checkbox"/>	has been transmitted by the International Bureau.			
	<input type="checkbox"/>	is not required, as the application was filed in the United States Receiving Office (RO/US)			
6.	<input type="checkbox"/>	A translation of the International Application into English (35 U.S.C. 371(c)(2)).			
7.	<input checked="" type="checkbox"/>	Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))			
	<input type="checkbox"/>	are transmitted herewith (required only if not transmitted by the International Bureau).			
	<input type="checkbox"/>	have been transmitted by the International Bureau.			
	<input type="checkbox"/>	have not been made; however, the time limit for making such amendments has NOT expired.			
	<input checked="" type="checkbox"/>	have not been made and will not be made.			
8.	<input type="checkbox"/>	A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).			
9.	<input type="checkbox"/>	An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4))			
10.	<input checked="" type="checkbox"/>	A copy of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).			
Items 11. to 16. below concern other document(s) or information included:					
11.	<input type="checkbox"/>	An Information Disclosure Statement under 37 CFR 1.97 and 1.98			
12.	<input type="checkbox"/>	An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.			
13.	<input checked="" type="checkbox"/>	A FIRST preliminary amendment.			
	<input type="checkbox"/>	A SECOND or SUBSEQUENT preliminary amendment			
14.	<input type="checkbox"/>	A substitute specification			
15.	<input type="checkbox"/>	A change of power of attorney and/or address letter			
16.	<input type="checkbox"/>	Other items or information:			

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U.S. APPLICATION NO (If known, see 37 C.F.R. 1.50) <b>UNASSIGNED 09/600631</b>		INTERNATIONAL APPLICATION NO <b>PCT/GB99/00223</b>		ATTORNEY'S DOCKET NUMBER <b>040283/0182</b>	
17. <input checked="" type="checkbox"/> The following fees are submitted:				<b>CALCULATIONS</b>	
Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO .....\$840.00					
International preliminary examination fee paid to USPTO (37 CFR 1.482) .....\$670.00					
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .....\$690.00					
Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO .....\$970.00					
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) .....\$96.00					
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				<b>\$840.00</b>	
Surcharge of \$130.00 for furnishing the oath or declaration later than 20 Months from the earliest claimed priority date (37 CFR 1.492(e))					
Claims	Number Filed	Included in Basic Fee	Extra Claims	Rate	
Total Claims	22	-	20	= 2	\$18.00
Independent Claims	1	-	3	= 0	\$78.00
Multiple dependent claim(s) (if applicable)					\$260.00
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$876.00</b>	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$0.00	
<b>SUBTOTAL =</b>				<b>\$876.00</b>	
Processing fee of \$130.00 for furnishing English translation later the 20 months from the earliest claimed priority date (37 CFR 1.492(f)).				+	
<b>TOTAL NATIONAL FEE =</b>				<b>\$876.00</b>	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +					
<b>TOTAL FEES ENCLOSED =</b>				<b>\$876.00</b>	
				Amount to be:	
				refunded \$	
				charged \$	
a. <input checked="" type="checkbox"/> A check in the amount of \$876.00 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. <u>19-0741</u> in the amount of \$-0- to the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>19-0741</u> . A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status					
SEND ALL CORRESPONDENCE TO:					
Foley & Lardner Washington Harbour 3000 K Street, N.W., Suite 500 Washington, D.C. 20007-5109			SIGNATURE  NAME BERNHARD D. SAXE		
REGISTRATION NUMBER 28,665					

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE***

Applicant: David Reginald ADAMS et al.  
Title: AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS  
DISORDERS  
Appl. No.: UNASSIGNED  
Filing Date: July 20, 2000  
Examiner: Not yet assigned  
Art Unit: Not yet assigned

**PRELIMINARY AMENDMENT**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Prior to examination of the present Application, Applicants respectfully request that the above-identified application be amended as follows:

**IN THE CLAIMS:**

**Please cancel Claims 18-22, in their entirety without prejudice or disclaimer.**

Claim 3, line 1, delete "or 2".

Claim 4, line 1, delete "any preceding claim" and insert --claim 1--.

Claim 6, line 1, delete ", 2, 3, 4 or 5".

Claim 8, line 1, delete ", 2, 3, 4 or 5".

Claim 12, line 1, delete "any one of claims 1 to 11" and insert --claim 1--.

Claim 13, line 1, delete "any one of claims 1 to 12" and insert --claim 1--.

Claim 14, line 1, delete "any one of claims 1 to 13" and insert --claim 1--.

Claim 15, line 1, delete "any one of claims 1 to 13" and insert --claim 1--.

Claim 16, line 1, delete "any one of claims 1 to 13" and insert --claim 1--.

Claim 23, lines 1 and 2, delete "any one of claims 1 to 17" and insert --claim 1--.

Claim 24, line 3, delete "any one of claims 1 to 17" and insert --claim 1--.

Claim 27, line 3, delete "any one of claims 1 to 17" and insert --claim 1--.

Claim 30, line 3, delete "any one of claims 1 to 22" and insert --claim 1--.


**REMARKS**

Applicants respectfully request that the foregoing amendments to Claims 3, 4, 6, 8, 12-16, 23, 24 and 27 be entered. These amendments are being made in order to avoid this application incurring a surcharge for the presence of one or more multiple dependent claims. No new matter has been added.

Respectfully submitted,

Date July 20, 2000

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By 

Bernhard D. Saxe  
Attorney for Applicant  
Registration No. 28,665

Rec'd PCT/PTO 20 JUL 2000

AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS

The present invention relates to chemical compounds useful in the treatment of disorders of the central nervous system (CNS), such as anxiety and all forms of epilepsy, particularly in humans. The invention also relates to the use of such compounds, pharmaceutical preparations containing such compounds and to methods of preparing such compounds.

Anxiety disorders affect an estimated 73 million people world-wide. The benzodiazepines have provided the dominant therapy for anxiety over the past three decades and there is no doubt that they are remarkably effective anxiolytics. However, chronic administration of benzodiazepines produces severe dependence liability, withdrawal syndromes, and side effects (sedation, amnesia, muscle relaxation). The only non-benzodiazepine anxiolytic that has been launched over the past decade is the 5-HT receptor ligand buspirone (Buspar®). This drug has had a remarkable commercial success despite being regarded as a weak anxiolytic (compared with the benzodiazepines) and having a long latency to onset of therapeutic action (2-4 weeks). In addition, buspirone and all related 5-HT<sub>1A</sub> partial agonists suffer from a dose-limiting side-effect profile comprising nausea, vertigo and endocrine changes.

The aetiology of anxiety disorders is not fully understood, but it is now established that benzodiazepines act by potentiating GABAergic neurotransmission although there is strong evidence that other neurotransmitter systems are modulated indirectly - in particular, the serotonergic and noradrenergic systems. Many pharmaceutical companies have invested considerable resource into the development of serotonergic anxiolytics. However, it is now apparent that ligands selective for 5-HT receptor subtypes, despite displaying anxiolytic-like activity in a restricted range of anxiety models, have, at best, very weak and/or non-dose-related anxiolytic effects in the clinic. The 5-HT<sub>3</sub> receptor antagonists are now discredited as psychotropics: they have a restricted range of activity in functional and anxiety models; they show no convincing anxiolytic effects in the clinic; and they are now accepted only as useful anti-emetics. The 5-HT<sub>2A</sub> antagonists similarly are regarded as ineffective in terms of psychotropic activity. The clinical utility of 5-HT<sub>1A</sub> receptor agonists and partial agonists is severely limited by their intrinsically weak action and by the dose-limiting side-effects (vertigo, endocrine changes, nausea) which become more intense as the agonist efficacy of these molecules is increased. The selective CCK<sub>B</sub> receptor antagonists have displayed an

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unimpressive preclinical profile similar to that of selective 5-HT ligands such as the 5-HT<sub>3</sub> antagonists.

Serotonergic anxiolytics include the selective serotonin reuptake inhibitors (SSRIs) which, in addition to displaying antidepressant properties, are also effective in anxiety disorders such as panic disorder and obsessive-compulsive disorder. However, as with their antidepressant action, the major drawback with these compounds is the long delay (6-8 weeks) in the onset of clinical improvement following chronic administration.

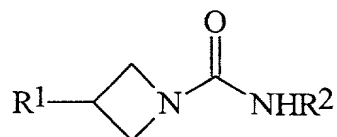
A strategy in recent years towards improving the clinical profile of classical benzodiazepines is that of developing benzodiazepine receptor partial agonists, according to the rationale that they would have a more selective anxiolytic action and be less liable to induce dependence. However, this approach appears to have failed owing to the very weak anxiolytic actions of these compounds and their poor side-effect profiles (there is either a low or non-existent ratio between anxiolytic and sedative doses).

US-4956359 and EP-A-0194112 disclose 3-aryloxy and 3-arylthio azetidinecarboxamides and their anti-convulsant and anti-epileptic activity. These compounds, like the benzodiazepines, have low water solubility which leads to difficulties in formulation. The presence of an oxygen or sulphur atom, present as a linking atom between the aryl group and the azetidine ring, is a key feature of these compounds since such atoms can undergo hydrogen-bonding interactions with other molecules, affect molecular conformation and increase electron density in the aryl rings.

There remains therefore a need for novel anxiolytic and anti-epileptic agents which do not suffer the above-mentioned drawbacks.

It has now been found that the oxygen and sulphur linking atoms are not necessary for pharmacological action. It is unexpected that compounds in which such atoms are absent exhibit pharmacological activity.

According to the present invention there is provided a chemical compound of formula (1)



(1)

wherein:

- 5 R<sup>1</sup> is aryl; and  
R<sup>2</sup> is hydrogen or alkyl;  
and pharmaceutically acceptable addition compounds thereof.

Reference in the present specification to an "alkyl" group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic or acyclic the alkyl group is preferably C<sub>1</sub> to C<sub>12</sub>, more preferably C<sub>1</sub> to C<sub>8</sub> (such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, amyl, isoamyl, hexyl, heptyl, octyl).

Reference in the present specification to an "aryl" group means a mono or bicyclic aromatic group, such as phenyl or naphthyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include:

carbon containing groups such as

alkyl

aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

- 25 halogen atoms and halogen containing groups such as

haloalkyl (e.g. trifluoromethyl);

oxygen containing groups such as

alcohols (e.g. hydroxy, hydroxyalkyl, (aryl)(hydroxy)alkyl),

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- ethers (e.g. alkoxy, alkoxyalkyl, aryloxyalkyl),  
 aldehydes (e.g. carboxaldehyde),  
 ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl,  
 arylalkylcarbonyl, arylcarbonylalkyl),  
 5 acids (e.g. carboxy, carboxyalkyl),  
 acid derivatives such as esters  
 (e.g. alkoxycarbonyl, alkoxycarbonylalkyl,  
 alkylcarbonyloxy, alkylcarbonyloxyalkyl)  
 and amides  
 10 (e.g. aminocarbonyl, mono- or dialkylaminocarbonyl,  
 aminocarbonylalkyl, mono- or  
 dialkylaminocarbonylalkyl, arylaminocarbonyl);  
 nitrogen containing groups such as  
 amines (e.g. amino, mono- or dialkylamino, aminoalkyl,  
 15 mono- or dialkylaminoalkyl),  
 azides,  
 nitriles (e.g. cyano, cyanoalkyl),  
 nitro;  
 sulphur containing groups such as  
 20 thiols, thioethers, sulphoxides and sulphones  
 (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl,  
 alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl,  
 arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl,  
 arylsulfinylalkyl, arylsulfonylalkyl); and  
 25 heterocyclic groups containing one or more, preferably one,  
 heteroatom,  
 (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl,  
 thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl,  
 pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl,  
 30 tetrahydrofuranyl, pyranal, pyronal, pyridyl,  
 pyrazinyl, pyridazinyl, piperidyl, piperazinyl,  
 morpholinyl, thionaphthyl, benzofuranyl,



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5 isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl).

Preferred substituents include alkyl, aryl, halo, or an halogen-containing group such as trifluoromethyl.

10 As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

15 The compounds of formula (1) may exist in a number of diastereomeric and/or enantiomeric forms. Reference in the present specification to "a compound of formula (1)" is a reference to all stereoisomeric forms of the compound and includes a reference to the unseparated stereoisomers in a mixture, racemic or non-racemic, and to each stereoisomer in its pure form.

20 In the compounds of formula (1), preferably  $R^1$  is a substituted or unsubstituted aryl group selected from phenyl and naphthyl, more preferably  $R^1$  is a substituted phenyl or naphthyl, more preferably  $R^1$  is phenyl or naphthyl having 1 to 3 substituents and most preferably  $R^1$  is phenyl or naphthyl having 1 or 2 substituents. In a preferred embodiment of the invention,  $R^1$  is a mono- or di-substituted phenyl group, preferably a mono-substituted phenyl group.

25 Where  $R^1$  is naphthyl, it is preferred that  $R^1$  is 2-naphthyl.

The preferred substituent groups are selected from halo (preferably fluoro and chloro), trifluoromethyl and tertiary butyl, and more preferably from fluoro, chloro and  
30 trifluoromethyl.

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Where  $R^1$  is a phenyl having 1 substituent, the phenyl group is preferably para- or meta-substituted. Where  $R^1$  is a phenyl having 2 substituents, the phenyl group is preferably 2,3-disubstituted, 2,4-disubstituted, 3,4-disubstituted or 3,5-disubstituted, preferably 3,4-disubstituted.

5

Where  $R^1$  is disubstituted, it is preferred that  $R^1$  is substituted by two halo groups, the same or different, or by one halo group and one trifluoromethyl group. More preferably,  $R^1$  is dichloro-, difluoro-, chloro-fluoro- or fluoro-trifluoromethyl-substituted.

10 The  $R^1$  groups are preferably selected from 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-(trifluoromethyl)phenyl, 4-fluoro-3-(trifluoromethyl)phenyl and 3-chloro-5-fluorophenyl.

15 In one embodiment of the present invention  $R^2$  is alkyl, preferably selected from  $C_{1-8}$  alkyl, more preferably from alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl and unsubstituted saturated cyclic and acyclic hydrocarbyl, and more preferably from propyl, 2-propenyl, 2-propynyl and 2-hydroxypropyl.

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Particularly preferred compounds are as follows:-

Chirality	R <sup>1</sup>	R <sup>2</sup>
-	4-Cl-C <sub>6</sub> H <sub>4</sub>	2-propenyl
-	4-F-C <sub>6</sub> H <sub>4</sub>	2-propenyl
-	4-F-C <sub>6</sub> H <sub>4</sub>	2-propynyl
R	4-F-C <sub>6</sub> H <sub>4</sub>	MeCH(OH)CH <sub>2</sub>
-	4-Cl-C <sub>6</sub> H <sub>4</sub>	2-propynyl
R	4-Cl-C <sub>6</sub> H <sub>4</sub>	MeCH(OH)CH <sub>2</sub>
S	4-F-C <sub>6</sub> H <sub>4</sub>	MeCH(OH)CH <sub>2</sub>
S	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	MeCH(OH)CH <sub>2</sub>
-	3-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	2-propynyl
-	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	2-propynyl
R	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	MeCH(OH)CH <sub>2</sub>
-	4-CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	H

- 5 Of these, the preferred compounds are: 3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide, (*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-Fluorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide, (*R*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-Chlorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide, (*S*)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(3-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide and 3-(4-(Trifluoromethyl)phenyl)-*N*-azetidine-1-carboxamide.
- 10

According to a further aspect of the present invention there is provided a compound according to the present invention for use in therapy.

- 5 The compounds of the present invention may be used in the treatment (including prophylaxis) of CNS disorders. In particular, the compounds of the present invention may be used in the treatment (including prophylaxis) of anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases (for example, senile dementia) and  
10 symptoms related to withdrawal from substance abuse. The compounds may also be used in the relief of spasticity. The compounds of the present invention may also be used in muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery.

- In a preferred embodiment of the present invention, the compounds are used in the treatment  
15 (including prophylaxis) of anxiety or epilepsy.

- Anxiety includes generalised anxiety disorder (GAD), panic disorder, panic disorder plus agoraphobia, simple (specific) phobias (e.g. arachnophobia, performance anxiety such as public speaking), social phobias, post-traumatic stress disorder, anxiety associated with  
20 depression, and obsessive compulsive disorder (OCD).

- Epilepsy is a chronic disorder characterised by recurrent seizures. Two forms of epilepsy exist - partial and generalised epilepsy - and each type is subdivided into idiopathic (cause unknown) or symptomatic (cause known). There are two fundamental types of seizures:  
25 partial seizures which includes simple partial seizures, complex partial seizures, and partial seizures secondarily generalised; and generalised seizures which includes generalised tonic-clonic seizures (grand mal), absence seizures (petit mal), myoclonic seizures, atonic seizures, clonic seizures, and tonic seizures.

- According to a further aspect of the present invention there is provided use of a compound of  
30 the present invention in the manufacture of a medicament for the treatment (including prophylaxis) of CNS disorders, preferably anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome,

chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse or spasticity, and more preferably anxiety or epilepsy.

According to a further aspect of the present invention there is provided use of a compound of  
5 the present invention in the manufacture of a medicament for muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery.

The invention further provides a method of treatment (including prophylaxis) of CNS disorders, preferably anxiety, epilepsy, insomnia, including travel insomnia and insomnia  
10 associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse and spasticity, and more preferably anxiety or epilepsy, comprising administering to a patient in need of such treatment an effective dose of a compound according to the present invention.

15 The invention further provides a method of muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery, comprising administering to a patient in need thereof an effective dose of a compound according to the present invention.

According to a further aspect of the present invention there is provided a method of preparing  
20 a compound of the present invention.

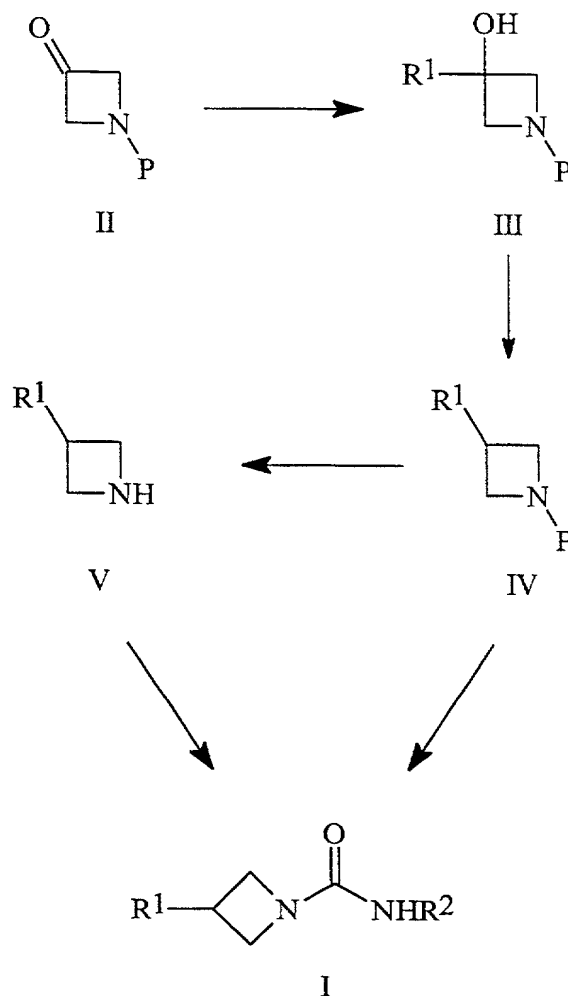
Compounds of the present invention may be prepared according to the reaction scheme (where P is a nitrogen protecting group).  $R^1$  and  $R^2$  are as previously defined. The 3-aryl-3-azetidinol (III) may be formed by treatment of the ketone (II) with an organometallic reagent  
25 such as an aryllithium or an arylmagnesium halide. Removal of the hydroxyl group to give the 3-arylazetidine (IV) may be effected by several methods including, for example, catalytic hydrogenolysis; treatment with lithium or sodium and ammonia; conversion to the xanthate by treatment with carbon disulphide, methyl iodide and base, followed by tin-mediated reduction; and conversion to the 3-aryl-3-chloroazetidine analogue using an alkylsulfonyl  
30 chloride and a base, followed by a reductive dechlorination using sodium, lithium or nickel. Formation of the azetidine (V) is achieved by reaction of (IV) with a suitable nitrogen deprotection agent. For example, if P is a diphenylmethyl group, then deprotection may be carried out by either catalytic transfer hydrogenation (e.g. ammonium formate and palladium

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catalyst) or by treatment with 1-chloroethyl chloroformate followed by methanol. The urea (I) is formed by reaction of azetidine (V) with an N-alkylisocyanate or an N-alkylcarbamoyl chloride and a base such as triethylamine or potassium carbonate. Alternatively, the urea may be prepared directly from the azetidine (IV) without isolation of an intermediate such as the secondary amine (V). For example, when P is a diphenylmethyl group, azetidine (IV) may be treated with phosgene followed by amine  $R^2NH_2$  to give urea (I) directly.

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## Reaction Scheme



The invention further provides a pharmaceutical composition comprising a compound according to the present invention in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound according to the present invention with a pharmaceutically acceptable carrier or excipient.

Compounds of the present invention may be administered in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use including transmucosal and transdermal use, for example a cream, ointment, gel, aqueous or oil solution or suspension, salve, patch or plaster; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration

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by inhalation, for example a finely divided powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oil solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients, using standard techniques well known to those skilled in the art of pharmacy. Preferably, the compound is administered orally.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.



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It will be appreciated that the dosage levels used may vary over quite a wide range depending upon the compound used, the severity of the symptoms exhibited by the patient and the patient's body weight.

- 5 The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the invention.

## **EXPERIMENTAL**

10

### **Antagonism of 3-MPA-Induced Seizures**

- Several animal seizure models are available for the screening and characterisation of anticonvulsant (antiepileptic) drugs. Most models employ a chemical convulsant to induce
- 15 seizures and the anticonvulsant potencies of novel compounds are measured in terms of their ability to increase the dose of convulsant required to induce a seizure response (or to prolong the latency to seizure onset following a bolus dose of the convulsant). Most chemical convulsants work by blocking the neurotransmitter function of gamma-aminobutyric acid (GABA), the predominant inhibitory neurotransmitter in the mammalian brain. This can be
- 20 achieved by blocking the postsynaptic action of GABA using pentylenetetrazol or bicuculline, or via a presynaptic action using a GABA synthesis inhibitor to decrease GABA release into the synapse. In this case, the inhibitor of glutamate decarboxylase (GAD), 3-mercaptopropionic acid (3-MPA), was used as the convulsant challenge agent. Anticonvulsant effects of test compounds were determined by their abilities to significantly
- 25 increase the dose of 3-MPA required to initiate a seizure response.

- Male albino T/O strain mice (obtained from Tuck) weighing 28-40 g were used in these studies. Animals were assigned randomly to treatment groups and vehicle or test drug (at a dose of 30mg/kg) were administered p.o. to groups of 12 animals 60 min before the
- 30 administration of a bolus dose of 3-MPA intravenously. Immediately following 3-MPA administration, each mouse was placed individually into a cage for observation. The seizure response of each animal was scored quantally as present or absent (response or non-response) during the 5 min period immediately following 3-MPA administration. A seizure response

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was defined as the onset of the initial clonic phase of the seizure (abrupt loss of righting reflex accompanied by vocalisation). The seizure threshold (in terms of mg/kg i.v. of 3-MPA required to evoke a seizure response) was determined in each treatment group by a sequential up/down method followed by modified probit analysis of the quantal data. A range of doses  
5 of 3-MPA was prepared (12.5 - 200.0 mg/kg i.v.) increasing by a constant geometric factor ( $^3\sqrt{2}$ ), which was found in pilot studies to generate suitable data for analysis by this method.

In these studies, 3-MPA was obtained from Sigma.

Test compounds were prepared as solutions dissolved in 45% w/v aqueous 2-hydroxypropyl-  
10  $\beta$ -cyclodextrin in distilled water. 3-MPA was dissolved in isotonic saline and its pH adjusted to 6 using 1M sodium hydroxide solution. Drugs were administered in a dose volume of 10 ml/kg body weight. The test results are shown in Table 1.

**Table 1 - Antagonism of 3-MPA-Induced Seizures: Results of Testing**

Compound	SC	SV
Example 1	42.7	15.7
Example 2	24.2	18.6
Example 3	21.4	18.6
Example 4	27.3	18.6
Example 5	32.4	15.7
Example 6	59.5	20.6
Example 7	54.4	20
Example 8	100	15.7
Example 9	29.7	14.9
Example 10	95.8	15.6
Example 15	58.4	14.1
Example 19	>200.0 <sup>a</sup>	17.2

SC = Seizure threshold after treatment with test drug

SV = Seizure threshold in vehicle-treated group

5    <sup>a</sup> = No seizures were observed at the top dose of 200mg/Kg i.v. of 3-MPA

#### **Measurement of anxiolytic activity in mice using the elevated zero-maze model.**

10    The elevated "zero-maze" is a modification of the elevated plus-maze model of anxiety which incorporates both traditional and novel ethological measures in the analysis of drug effects (Shepherd, J.K., Grewal, S.S., Fletcher, A., Bill, D.J. and Dourish, C.T., Behavioural and pharmacological characterisation of the elevated "zero-maze" as an animal model of anxiety. *Psychopharmacology*, 1994, 116, 56-64).

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Male Sprague-Dawley rats (Charles River) weighing 300-450 gm are used. Animals are group-housed (5 per cage; cage size: 40 x 40 x 20 cm) in a temperature-controlled environment ( $20\pm 2^{\circ}\text{C}$ ), under a 12h light-dark cycle (lights on: 08:00 hours). Food and water are made freely available. Four hours prior to testing, animals are transferred to clean cages and moved to the testing room in order to habituate to the testing environment.

The maze is comprised of a black Perspex annular platform (105cm diameter, 10cm width) elevated to 65cm above ground level, divided equally into four quadrants. Two opposite quadrants are enclosed by clear red Perspex walls (27cm high) on both the inner and outer edges of the platform, while the remaining two opposite quadrants are surrounded only by a Perspex "lip" (1cm high) which serves as a tactile guide to animals on these open areas. To facilitate the measurement of locomotor activity, the apparatus is divided into octants by splitting each quadrant into equal halves using high contrast white lines. The apparatus is illuminated by dim red lighting arranged in such a manner as to provide similar lux levels in both the open and closed quadrants (40-60 lux). A video camera, connected to a VCR in an adjacent observation room, is mounted overhead in order to record behaviour on the maze for subsequent analysis.

Chlordiazepoxide hydrochloride [CDP; Sigma Chemical Co. Ltd., Poole], which has previously been shown to display robust anxiolytic-like effects in the zero-maze, serves as positive control. Drugs are typically dissolved in a 45% solution of 2-hydroxy-propyl- $\beta$ -cyclodextrin, and administered orally by gavage 1 hour prior to zero-maze testing.

Rats are placed on a closed quadrant and a 5 min test period is recorded on video-tape. The maze is cleaned with a 5% methanol/water solution and dried thoroughly between test sessions. Five behavioural parameters are scored: [1] percentage of time spent on the open areas; [2] frequency of head dips over the edge of the platform when subjects are located in either the open or the end of the closed quadrants; [3] frequency of stretch-attend postures (SAP) from closed to open quadrants, determined when the subject, on a closed quadrant, exhibits an elongated body posture stretched forward with at least the snout passing over the open/close divide; [4] frequency of rearing; and [5] the number of line crossings. Animals are scored as being in the open area when all four paws were in an open quadrant, and in the

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closed area only when all four paws passed over the open/closed divide. All testing is carried out between 1100 and 1700 hours.

An increase in the frequency of head dips is considered to be a measure of anxiolytic activity.

- 5 The compound of example 6 was found to be effective at a dose of 100 mg/Kg.

## CHEMISTRY

### 10 1-(Diphenylmethyl)-3-azetidinol (2)

The compound (2) was prepared according to the method of Anderson and Lok (*J. Org. Chem.* **1972**, 37, 3953, the disclosure of which is incorporated herein by reference), m.p. 111-112 °C (lit. m.p. 113 °C).

15

### 1-Diphenylmethyl-3-azetidinone (3)

- Dimethyl sulfoxide (0.36 mL, 5 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.40 mL, 4.6 mmol) in dichloromethane (20 mL) at -78 °C under an argon atmosphere. The mixture was stirred for 10 minutes then a solution of 1-(diphenylmethyl)-3-azetidinol (1.0 g, 4.2 mmol) in dichloromethane (20 mL) was added dropwise. The mixture was warmed to -50 °C and stirred for 30 minutes. Triethylamine (2.9 mL, 21 mmol) was added and the mixture warmed to room temperature. After 1 hour, water (50 mL) was added and the mixture extracted with dichloromethane (4 x 50 mL). The combined organic extracts were washed (brine), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give 1-diphenylmethyl-3-azetidinone (3) as a pale yellow crystalline solid (1.0 g, 99 %) (lit. (S.S. Chatterjee and A. Shoenb, *Synthesis*, 1973,153) m.p. 82°C).

### 3-(4-Chlorophenyl)-1-(diphenylmethyl)-3-azetidinol (4)

- 30 To a stirred solution of 4-chlorophenylmagnesium bromide (9.1 mL, 1.0M in diethyl ether) in diethyl ether (80 mL) at -78 °C under an argon atmosphere was added compound 3 (1.8 g, 7.6 mmol) in diethyl ether (50 mL) dropwise over 20 minutes. The reaction mixture was stirred at -78 °C for 2 hours, then slowly warmed to room temperature with stirring over 18

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hours. The reaction mixture was then partitioned between aqueous ammonium acetate solution (50 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed (water, brine), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo* to give the crude product as a pale yellow viscous oil in quantitative yield. A sample purified for analysis by column chromatography on silica gel using 15-30% ethyl acetate-hexane as eluent and subsequent crystallisation from hexane gave 3-(4-chlorophenyl)-1-(diphenylmethyl)-3-azetidinol (4), m.p. 108°C. Found: C, 75.42; H, 5.79; N, 3.98.  $\text{C}_{22}\text{H}_{20}\text{ClNO}$  requires C, 75.53; H, 5.76; N, 4.00%.

10 **O-(3-(3-(4-Chlorophenyl)-1-diphenylmethyl))azetidiny)-S-methyldithiocarbonate (5)**

To a stirred suspension of sodium hydride (0.4 g of a 60% suspension in mineral oil, 10.4 mmol) (prewashed with hexane) in THF (80 mL) was added dropwise a solution of compound 4 (1.7 g, 4.9 mmol) in THF (80 mL). The mixture was stirred for 3 hours then carbon disulphide (17.6 mL, 0.29 mol) and methyl iodide (6.1 mL, 0.1 mol) were added dropwise. The mixture was stirred at room temperature for 15 hours and then heated to 50 °C while the solvent was removed in a stream of argon. When the volume of the mixture was reduced by half, the mixture was concentrated *in vacuo* to an approximate volume of 20 mL and then partitioned between water and diethyl ether. The organic layer was washed with water and then brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated *in vacuo*. The crude product was crystallised from hexane to give O-(3-(3-(4-chlorophenyl)-1-diphenylmethyl))azetidiny)-S-methyldithiocarbonate (5) (2.06g, 96%).

25 **3-(4-Chlorophenyl)-1-(diphenylmethyl)azetidine (6)**

To a stirred solution of tributyltin hydride (1.8 mL, 6.9 mmol) in dry toluene (40 mL) at reflux under an argon atmosphere was added dropwise, over 1 hour, a solution of compound 5 (2.0 g, 4.6 mmol) in toluene (40 mL). The mixture was heated under reflux for a further 2 hours then was concentrated *in vacuo*. The residue obtained was purified by flash column chromatography on silica gel using hexane and then 10% ethyl acetate-hexane as eluent. The product was recrystallised twice from hexane to give 3-(4-chlorophenyl)-1-(diphenylmethyl)azetidine (6) (0.4 g, 34%) m.p. 82 °C. Found: C, 78.94; H, 6.06; N, 4.14.  $\text{C}_{22}\text{H}_{20}\text{ClN}$  requires C, 79.15; H, 6.04; N, 4.20%.

**3-(4-Chlorophenyl)azetidine (7)**

To a solution of compound 6 (0.36 g, 1.1 mmol) in 1,2-dichloroethane (10 mL) containing proton sponge (0.02 g), cooled in an ice-water bath under an argon atmosphere, was added dropwise 1-chloroethyl chloroformate (0.3 mL, 3.1 mmol). The resultant solution was boiled at reflux for 4 hours, cooled and was concentrated *in vacuo*. The residue obtained was mixed with methanol (10 mL) and heated under reflux for 2 hours, then cooled and concentrated *in vacuo* to give the hydrochloride salt of 3-(4-chlorophenyl)azetidine (7) which was used without further purification.

**Example 1. 3-(4-Chlorophenyl)-N-(2-propenyl)azetidine-1-carboxamide (8)**

To the hydrochloride salt of 3-(4-chlorophenyl)azetidine (7) (approximately 1.1 mmol) in ethanol (10 mL) stirred at 0°C was added sequentially and dropwise allyl isocyanate (0.15 mL, 1.7 mmol) followed by triethylamine (0.3 mL, 2.2 mmol). After 20 minutes the reaction mixture was partitioned between aqueous ammonium chloride and ether. The organic layer was washed (water and then brine), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated *in vacuo* to give a crude product. The product obtained was purified by column chromatography on silica gel using 20% ethyl acetate-hexane as eluent to give 3-(4-chlorophenyl)-N-(2-propenyl)azetidine-1-carboxamide (8) which was recrystallised from cyclohexane/toluene (0.16 g, 61%), m.p. 112 °C. Found: C, 62.20; H, 6.23; N, 11.40. C<sub>13</sub>H<sub>15</sub>ClN<sub>2</sub>O requires C, 62.28; H, 6.03; N, 11.17%.

**3-(4-tert-Butylphenyl)-1-diphenylmethyl-3-azetidinol (9)**

To a stirred solution of 4-tert-butylphenylmagnesium bromide (11.5 mL, 2.0M (Et<sub>2</sub>O)) in toluene (50 mL) at -78°C under argon, was added, dropwise, a solution of 1-diphenylmethyl-3-azetidinone (3) (5.0 g) in toluene (100 mL) over 30 minutes. The mixture was stirred for 4 hours at -78°C then warmed to room temperature and partitioned between aqueous ammonium chloride solution (50 mL) and diethyl ether (3 x 50 mL). The combined organic fractions were washed (water, brine), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Recrystallisation from cyclohexane gave 3-(4-tert-butylphenyl)-1-diphenylmethyl-3-

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azetidinol (9) (6.23 g), m.p. 168-169°C (cyclohexane). Found: C, 83.68; H, 7.97; N, 3.72.  $C_{26}H_{29}NO$  requires C, 84.06; H, 7.87; N, 3.77%.

### 3-(4-tert-Butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10)

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To a stirred solution of compound (9) (6.23 g) and N,N-diisopropylethylamine (3.5 mL) in dichloromethane (100 mL) at 0°C was added, dropwise, methanesulfonyl chloride (1.4 mL). The mixture was stirred at 0°C for 18 hrs, then washed (water, brine), dried ( $Na_2SO_4$ ) and concentrated in vacuo. The crude product was recrystallised from hexane to give 3-(4-tert-butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10) (4.73 g) m.p. 145°C (hexane). Found: C, 80.30; H, 7.05; N, 3.64.  $C_{26}H_{28}ClN$  requires C, 80.08; H, 7.24; N, 3.59%.

10

### 3-(4-tert-Butylphenyl)-1-(diphenylmethyl)azetidine (11)

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To a stirred suspension of Raney Nickel (8.6 g, wet slurry) in tertiary butanol (50 mL) and toluene (50 mL) was added a solution of 3-(4-tert-butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10) (4.73 g) in toluene (10 mL). The mixture was heated to 80°C for 6 hours, cooled to room temperature and filtered through kieselguhr. The filtrate was concentrated in vacuo and partitioned between diethyl ether (3 x 50 mL) and aqueous potassium carbonate solution (50 mL). The combined organic extracts were washed (water, brine), dried ( $Na_2SO_4$ ), concentrated in vacuo and purified by flash column chromatography (10% ethyl acetate/hexane) on silica. Recrystallisation from methanol gave 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (3.40 g), m.p. 95°C (methanol). Found: C, 87.84; H, 8.17; N, 3.92.  $C_{26}H_{29}N$  requires C, 87.84; H, 8.22; N, 3.94%.

20

### Example 2. 3-(4-tert-Butylphenyl)-N-(2-propenyl)azetidine-1-carboxamide (12)

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To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (1.0 g) in dichloromethane (10 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (2.5 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (10 mL) and to this solution at 0°C was added, dropwise, with stirring, allylamine (0.8 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (30 mL), washed (water, brine), dried ( $Na_2SO_4$ ),

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concentrated in vacuo and purified by flash column chromatography (50% ethyl acetate-hexane) to give 3-(4-tert-butylphenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (12) (0.21 g), m.p. 98-99°C (diisopropyl ether). Found: C, 74.95; H, 8.97; N, 10.25.  $C_{17}H_{24}N_2O$  requires C, 74.96; H, 8.88; N, 10.28%.

5

**Example 3. 3-(4-tert-Butylphenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (13)**

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (0.5 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (0.8 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring propargylamine (0.24 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried ( $Na_2SO_4$ ) and concentrated in vacuo. Trituration with diethyl ether (2 mL) gave 3-(4-tert-butylphenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (13) (0.14 g), m.p. 141°C (diethyl ether). Found: C, 75.40; H, 8.19; N, 10.38.  $C_{17}H_{22}N_2O$  requires C, 75.52; H, 8.20; N, 10.36%.

**Example 4. (R)-3-(4-tert-Butylphenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (14)**

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (0.50 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (0.8 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring (R)-1-amino-2-propanol (0.25 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried ( $Na_2SO_4$ ) concentrated in vacuo and purified by flash column chromatography (10% methanol-ethyl acetate) to give (R)-3-(4-tert-butylphenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (14) (0.35 g), m.p. 96-97°C (diisopropyl ether). Found: C, 69.59; H, 8.74; N, 9.23.  $C_{17}H_{26}N_2O$  requires C, 70.31; H, 9.02; N, 9.64%.

**3-(4-Fluorophenyl)-1-diphenylmethyl-3-azetidinol (15)**

To a stirred solution of 4-fluorophenylmagnesium bromide (7.0 mL, 1.0M (Et<sub>2</sub>O)) in toluene (20 mL) at -78°C under argon, was added, dropwise, a solution of 1-diphenylmethyl-3-azetidinone (3) (1.4 g) in toluene (30 mL) over 30 minutes. The mixture was stirred for 4 hours at -78°C then warmed to room temperature and partitioned between aqueous ammonium chloride solution (50 mL) and diethyl ether (3 x 20 mL). The combined organic fractions were washed (water, brine), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. Purification by flash column chromatography (20% ethyl acetate, hexane) gave 3-(4-fluorophenyl)-1-diphenylmethyl-3-azetidinol (15) (1.82 g). To a stirred solution of the free base (1.82 g) in ether (5 mL) was added dropwise a solution of oxalic acid (0.49 g) in acetone (1 mL). The mixture was stirred for 5 minutes then filtered to give the oxalate salt hemihydrate (2.23 g), m.p. 75°C (acetone). Found: C, 66.71; H, 5.34; N, 3.04. C<sub>24</sub>H<sub>22</sub>FNO<sub>5</sub>·0.5H<sub>2</sub>O requires C, 66.67; H, 5.32; N, 3.17%.

**3-(4-Fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16)**

To a stirred solution of 3-(4-fluorophenyl)-1-diphenylmethyl-3-azetidinol (15) (4.0 g) and N,N-diisopropylethylamine (3.2 mL) in dichloromethane (100 mL) at 0°C was added, dropwise, methanesulfonyl chloride (1.25 mL). The mixture was stirred at 0°C for 18 hrs, then washed (water, brine) and dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The crude product was recrystallised from hexane to give 3-(4-fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16) (2.2 g), m.p. 108-109°C (hexane). Found: C, 75.13; H, 5.46; N, 3.93. C<sub>22</sub>H<sub>19</sub>ClFN requires C, 75.10; H, 5.44; N, 3.98%.

**3-(4-Fluorophenyl)-1-(diphenylmethyl)azetidine (17)**

To a stirred suspension of Raney Nickel (2.0 g, wet slurry) in tertiary butanol (10 mL) and toluene (50 mL) was added a solution of 3-(4-fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16) (1.9 g) in toluene (20 mL). The mixture was heated to 80°C for 6 hours, cooled and filtered through kieselguhr. The filtrate was concentrated in vacuo and partitioned between diethyl ether (3 x 30 mL) and aqueous potassium carbonate solution (50 mL). The combined organic extracts were washed (water, brine), dried (Na<sub>2</sub>SO<sub>4</sub>), and

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concentrated in vacuo. Recrystallisation from diisopropyl ether gave 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (1.5 g), m.p. 65-66°C (diisopropyl ether). Found: C, 83.25; H, 6.35; N, 4.41.  $C_{22}H_{20}FN$  requires C, 83.25; H, 6.35; N, 4.41%.

5

**Example 5. 3-(4-Fluorophenyl)-N-(2-propenyl)azetidine-1-carboxamide (18)**

10 To a stirred solution of 3-(4-fluorophenyl)-N-(diphenylmethyl)azetidine (17) (0.67 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (2.5 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added, dropwise, with stirring, allylamine (0.5 mL). The mixture was stirred for 18 hrs at room  
15 temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried ( $Na_2SO_4$ ) and concentrated in vacuo. Recrystallisation from diisopropyl ether gave 3-(4-fluorophenyl)-N-(2-propenyl)azetidine-1-carboxamide (18) (0.30g), m.p. 119-120°C (diisopropyl ether). Found: C, 66.61; H, 6.37; N, 11.74.  $C_{13}H_{15}FN_2O$  requires C, 66.65; H, 6.45; N, 11.95%.

20

**Example 6. 3-(4-Fluorophenyl)-N-(2-propynyl)azetidine-1-carboxamide (19)**

To a stirred solution of 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (0.38 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene  
25 (1.4 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added, dropwise, with stirring propargylamine (0.3 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried ( $Na_2SO_4$ ) and concentrated in vacuo. The crude material was purified by flash column chromatography  
30 (50% ethyl acetate hexane) and then crystallised from diisopropyl ether to give 3-(4-fluorophenyl)-N-(2-propynyl)azetidine-1-carboxamide (19) (0.14g), m.p. 141°C

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(diisopropyl ether). Found: C, 67.32; H, 5.65; N, 11.93.  $C_{13}H_{13}FN_2O$  requires C, 67.23; H, 5.64; N, 12.06%.

**Example 7. (R)-3-(4-Fluorophenyl)-N-(2-hydroxypropyl)azetidine-1-carboxamide (20)**

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To a stirred solution of 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (0.35 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (1.2 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring (R)-1-amino-2-propanol (0.2 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried ( $Na_2SO_4$ ) and concentrated in vacuo. The crude product was purified by flash column chromatography (10% methanol-ethyl acetate) to give (R)-3-(4-fluorophenyl)-N-(2-hydroxypropyl)azetidine-1-carboxamide (20) (0.21g), m.p. 104-105 °C (toluene/ethanol).  
15 Found: C, 61.93; H, 6.97; N, 10.9.  $C_{13}H_{17}FN_2O_2$  requires C, 61.89; H, 6.79; N, 11.10%.

**Example 8. (3-(4-Chlorophenyl)-N-(2-propynyl)azetidine-1-carboxamide (21)**

This compound was prepared from 3-(4-chlorophenyl)-1-(diphenylmethyl)azetidine (6) and propargylamine using the procedure outlined in Example 3, m.p. 160 °C (diethyl ether).  
20 Found C, 62.85; H, 5.38; N, 10.89  $C_{13}H_{13}ClN_2O$  requires C, 62.78; H, 5.27; N, 11.26%.

**Example 9. (R)-3-(4-Chlorophenyl)-N-(2-hydroxypropyl)azetidine-1-carboxamide (22)**

This compound was prepared from compound (6) and (R)-1-amino-2-propanol using the procedure outlined in Example 4, m.p. 92-93 °C (diethyl ether-toluene). Found: C, 58.97; H, 6.38; N, 9.96.  $C_{13}H_{17}ClN_2O_2 \cdot 0.2PhCH_3$ , requires C, 60.23; H, 6.48; N, 9.76%.

**Example 10: (S)-3-(4-Fluorophenyl)-N-(2-hydroxypropyl)azetidine-1-carboxamide (23)**

This compound was prepared from compound (17) and (S)-1-amino-2-propanol using the procedure described for compound (20). m.p. 102-104°C. Found: C, 61.94; H, 6.72; N, 11.1.  $C_{13}H_{17}FN_2O_2$  requires C, 61.89; H, 6.79; N, 11.10%.

**3-(3,4-Dichlorophenyl)-1-(diphenylmethyl)azetidin-3-ol (24)**

This compound was prepared from compound (3) and 3,4-dichlorophenylmagnesium  
5 bromide using the procedure described for compound (4).

**3-(3,4-Dichlorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (25)**

This compound was prepared from compound (24) using the procedure described for  
10 compound (10).

**3-(3,4-Dichlorophenyl)-1-(diphenylmethyl)azetidine (26)**

This compound was prepared from compound (25) using the procedure described from  
compound (11).

**Example 11. 3-(3,4-Dichlorophenyl)-N-(2-propynyl)azetidine carboxamide (27)**

15 This compound was prepared from compound (26) and propargylamine using the procedure  
described for compound (12). m.p. 105.5-107.5°C.

**Example 12. (R)-3-(3,4-Dichlorophenyl)-N-(2-hydroxypropyl)azetidine carboxamide (28)**

This compound was prepared from compound (26) and (R)-1-amino-2-propanol using the  
20 procedure described for compound (12). m.p. 123-125°C. Found: C, 51.58; H, 5.33; N, 9.26.  
C<sub>13</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> requires C, 51.50; H, 5.32; N, 9.24%.

**Example 13. (S)-3-(3,4-Dichlorophenyl)-N-(2-hydroxypropyl)azetidine carboxamide (29)**

25 This compound was prepared from compound (26) and (S)-1-amino-2-propanol using the  
procedure described for compound (12). m.p. 123-125°C. Found: C, 51.47; H, 5.30; N,  
9.18. C<sub>13</sub>H<sub>16</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> requires C, 51.50; H, 5.32; N, 9.24%.

**3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidin-3-ol (30)**

This compound was prepared from compound (3) and 4-(trifluoromethyl)phenylmagnesium bromide using the procedure described for compound (4).

**3-Chloro-3-(4-(trifluoromethyl)phenyl)-(diphenylmethyl)azetidine (31)**

- 5 This compound was prepared from compound (30) using the procedure described for compound (10).

**3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (32)**

This compound was prepared from compound (31) using the procedure described for compound (11).

- 10 **Example 14. (R)-3-(4-(Trifluoromethyl)phenyl)-N-(2-hydroxypropyl)azetidine carboxamide (33)**

This compound was prepared from compound (32) and (R)-1-amino-2-propanol using the procedure described for compound (12). m.p. 107-108°C. Found: C, 54.78; H, 5.75; N, 9.01. C<sub>14</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>·0.25 H<sub>2</sub>O requires C, 54.81; H, 5.71; N, 9.13%.

- 15 **Example 15. (S)-3-(4-(Trifluoromethyl)phenyl)-N-(2-hydroxypropyl)azetidine carboxamide (34)**

- 20 This compound was prepared from compound (32) and (S)-1-amino-2-propanol using the procedure described for compound (12). m.p. 107-108°C. Found: C, 54.75; H, 5.68; N, 9.09. C<sub>14</sub>H<sub>17</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>·0.25 H<sub>2</sub>O requires C, 54.81; H, 5.71; N, 9.13%.

**Example 16. 3-(4-(Trifluoromethyl)phenyl)-N-(2-propynyl)azetidine-1-carboxamide (35)**

- 25 This product was prepared from compound (32) and propargylamine using the procedure described for compound (12). m.p. 151-155°C.

**3-(3-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidin-3-ol (36)**

This compound was prepared from compound (3) and 3-(trifluoromethyl)phenylmagnesium bromide using the procedure described for compound (4).

**5 3-Chloro-3-(3-(trifluoromethyl)phenyl)-(diphenylmethyl)azetidine (37)**

This compound was prepared from compound (32) using the procedure described for compound (10).

**10 3-(3-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (38)**

This compound was prepared from compound (37) using the procedure described for compound (11).

**15 Example 17. (R)-3-(3-(Trifluoromethyl)phenyl)-N-(2-hydroxypropyl)azetidine carboxamide (39)**

This compound was prepared from compound (38) and (R)-1-amino-2-propanol using the procedure described for compound (12). m.p. 81-82°C.

20

**Example 18. (S)-3-(3-(Trifluoromethyl)phenyl)-N-(2-hydroxypropyl)azetidine carboxamide (40)**

This compound was prepared from compound (38) and (S)-1-amino-2-propanol using the procedure described for compound (12). m.p. 80-82°C.

25

**Example 19. 3-(3-(Trifluoromethyl)phenyl)-N-(2-propynyl)azetidine-1-carboxamide (41)**

This product was prepared from compound (38) and propargylamine using the procedure described for compound (12). m.p. 121°C.

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-28-

**Example 20. 3-(4-(Trifluoromethyl)phenyl)-N-azetidine-1-carboxamide (42)**

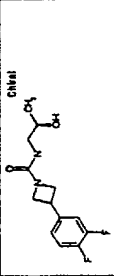
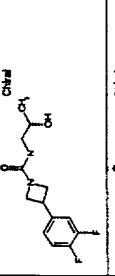
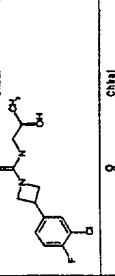
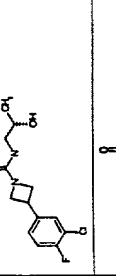
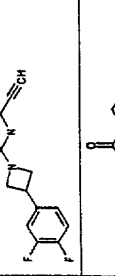
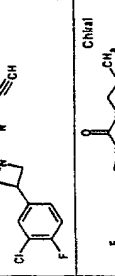
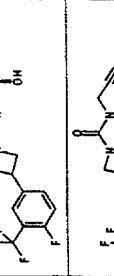
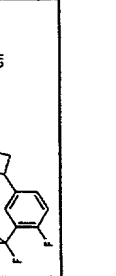
To a solution of 3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (32) (8.2 mmol) in dichloromethane (20 mL) at 0°C, was added a solution of phosgene (1.75M in toluene, 10.2 mmol). The reaction mixture was stirred at room temperature for 90 minutes, concentrated *in vacuo*, then redissolved in THF (25 mL), cooled to 0°C and treated with ammonium hydroxide (12.5 mL). The reaction was stirred for 16 h, then water (80 mL) and ethyl acetate (100 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL), combined organic layers washed with brine (60 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was triturated using ethyl acetate (60 mL) to a solid (1.64 g, 81%), mp. 207.5-208.5-°C (ethyl acetate). Found: C, 54.51; H, 4.59; N, 11.41. C<sub>14</sub>H<sub>17</sub>ClN<sub>2</sub>O<sub>2</sub> requires: C, 54.10; H, 4.54; N, 11.47.

**15 Examples 21 to 84 – See Table 2**

These products were prepared using the procedure described for compound 12.



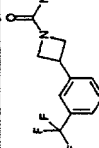
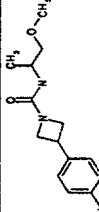
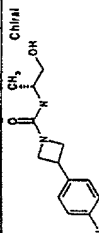
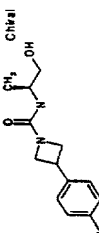

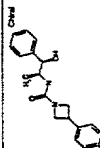
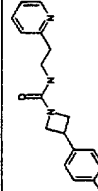
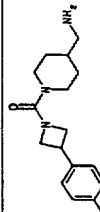
Table 2

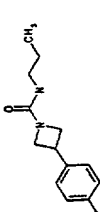
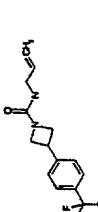
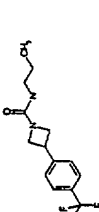
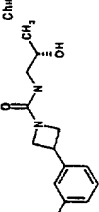
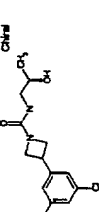
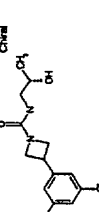
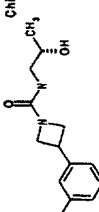
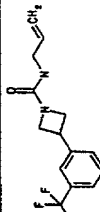
Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
21	43		C <sub>13</sub> H <sub>16</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	270.28	108-109	57.79	5.96	10.28	57.77	5.97	10.36	
22	44		C <sub>13</sub> H <sub>16</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	270.28	108-109	57.73	5.95	10.29	57.77	5.97	10.36	
23	45		C <sub>13</sub> H <sub>16</sub> ClF <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	286.74	83-84	54.44	5.65	9.74	54.46	5.62	9.77	
24	46		C <sub>13</sub> H <sub>16</sub> ClF <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	286.74	83-84	54.46	5.69	9.63	54.46	5.62	9.77	
25	47		C <sub>13</sub> H <sub>12</sub> F <sub>2</sub> N <sub>2</sub> O	250.25	123.0	62.36	4.81	11.20	62.40	4.83	11.19	
26	48		C <sub>13</sub> H <sub>12</sub> ClF <sub>2</sub> N <sub>2</sub> O	266.70	133.0	58.56	4.53	10.45	58.55	4.53	10.50	
27	49		C <sub>14</sub> H <sub>16</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>	320.29	69-71	52.44	5.02	8.69	52.50	5.03	8.74	
28	50		C <sub>14</sub> H <sub>12</sub> F <sub>4</sub> N <sub>2</sub> O	300.26	119.0	56.05	4.02	9.26	56.00	4.03	9.33	

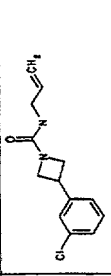
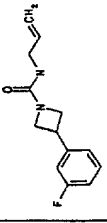
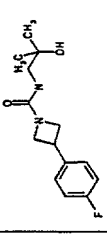
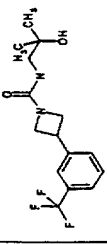
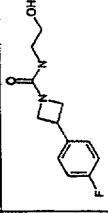
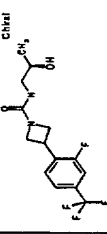
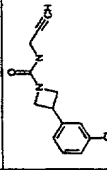
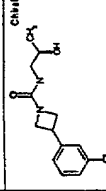
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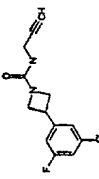
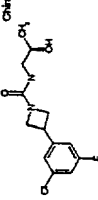
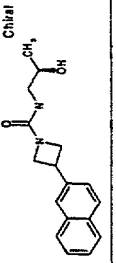
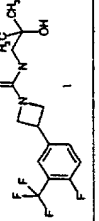
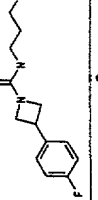
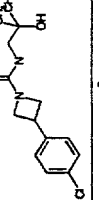
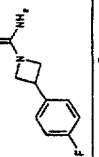
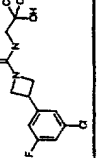
Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
29	51		C <sub>14</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>2</sub>	282.77	102.0	59.69	6.69	9.80	59.47	6.77	9.90	
30	52		C <sub>13</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	286.74	oil							α
31	53		C <sub>13</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub> O	266.70	132.0	58.53	4.58	10.45	58.55	4.53	10.50	
32	54		C <sub>14</sub> H <sub>17</sub> F <sub>3</sub> N <sub>2</sub> O <sub>2</sub>	302.30	89.0	55.65	5.64	9.20	55.63	5.67	9.26	
33	55		C <sub>14</sub> H <sub>13</sub> F <sub>3</sub> N <sub>2</sub> O	282.27	101.0	59.70	4.55	9.96	59.57	4.64	9.92	
34	56		C <sub>13</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub>	268.75	109.0	57.15	6.35	10.28	58.10	6.38	10.42	
35	57		C <sub>13</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	303.19	111.0	51.43	5.24	9.19	51.50	5.32	9.24	
36	58		C <sub>13</sub> H <sub>16</sub> F <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	270.28	88-89	57.74	6.11	10.34	57.77	5.97	10.36	

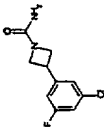
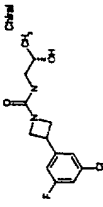
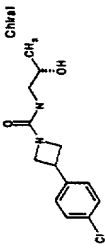
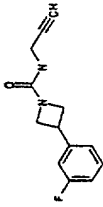
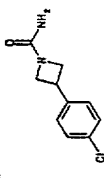
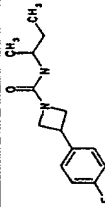
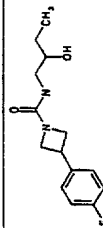
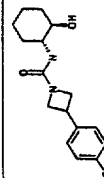
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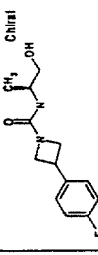
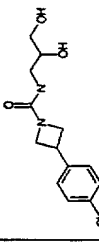
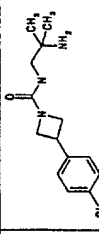
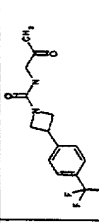
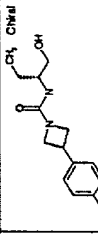
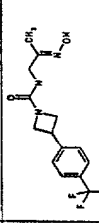
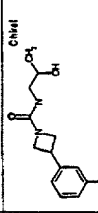
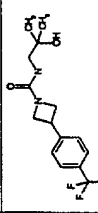
Example No.	Compound No.	Structure	Formula	MWt	mp	C <sub>found</sub>	H <sub>found</sub>	N <sub>found</sub>	C <sub>exp</sub>	H <sub>exp</sub>	N <sub>exp</sub>	Note
37	59		C <sub>11</sub> H <sub>11</sub> F <sub>2</sub> N <sub>2</sub> O	244.22	198.0	54.14	4.55	11.47	54.10	4.54	11.47	
38	60		C <sub>14</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>2</sub>	282.77	110.0	59.33	6.79	9.95	59.47	6.77	9.90	
39	61		C <sub>13</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub>	268.75	71-75							b
40	62		C <sub>13</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub>	268.75	82-85	58.09	6.41	10.36	58.10	6.38	10.42	
41	63		C <sub>14</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>2</sub>	282.77	134-135	59.31	6.86	10.02	59.47	6.77	9.90	
42	64		C <sub>19</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>2</sub>	344.84	120-122							c
43	65		C <sub>17</sub> H <sub>18</sub> ClN <sub>3</sub> O	315.81	125.0	64.75	5.74	13.27	64.66	5.74	13.30	
44	66		C <sub>16</sub> H <sub>22</sub> ClN <sub>3</sub> O	307.83	137-138	49.82	6.33	10.13	50.55	6.49	10.40	

Example No.	Compound No.	Structure	Formula	MWt	mp	C <sub>10</sub> und	H <sub>10</sub> und	N <sub>10</sub> und	C <sub>exp</sub>	H <sub>exp</sub>	N <sub>exp</sub>	Note
45	67		C <sub>13</sub> H <sub>17</sub> N <sub>2</sub> O	236.29	117-118.5	66.12	7.18	11.83	66.08	7.25	11.86	
46	68		C <sub>14</sub> H <sub>15</sub> F <sub>3</sub> N <sub>2</sub> O	284.28	136-137.5	59.26	5.39	9.93	59.15	5.32	9.85	
47	69		C <sub>14</sub> H <sub>17</sub> F <sub>3</sub> N <sub>2</sub> O	286.30	127-128.5	58.69	5.89	10.03	58.73	5.98	9.78	
48	70		C <sub>13</sub> H <sub>17</sub> N <sub>2</sub> O <sub>2</sub>	252.29	79.5-80	61.91	6.77	11.09	61.89	6.79	11.10	
49	71		C <sub>13</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	303.19	110-111	51.67	5.35	9.21	51.50	5.32	9.24	
50	72		C <sub>13</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	303.19	110-111	52.00	5.41	9.24	51.50	5.32	9.24	
51	73		C <sub>13</sub> H <sub>17</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	268.75	78-80	58.44	6.13	10.39	58.10	6.38	10.42	
52	74		C <sub>14</sub> H <sub>15</sub> F <sub>3</sub> N <sub>2</sub> O	284.28	64-66	58.94	5.32	10.15	59.15	5.32	9.85	

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
53	75		C <sub>13</sub> H <sub>15</sub> ClN <sub>2</sub> O	250.73	65-66	62.75	5.97	11.09	62.28	6.03	11.17	
54	76		C <sub>13</sub> H <sub>15</sub> FN <sub>2</sub> O	234.28	62.5-63.5	66.52	6.52	11.90	66.65	6.45	11.95	
55	77		C <sub>14</sub> H <sub>19</sub> FN <sub>2</sub> O <sub>2</sub>	266.32	77-78.5	63.25	7.25	10.52	63.14	7.19	10.51	
56	78		C <sub>15</sub> H <sub>19</sub> F <sub>3</sub> N <sub>2</sub> O <sub>2</sub>	316.33	94.5-96	57.00	5.85	8.82	56.96	6.05	8.85	
57	79		C <sub>12</sub> H <sub>15</sub> FN <sub>2</sub> O <sub>2</sub>	238.26	99-101	60.41	6.35	11.72	60.49	6.35	11.75	
58	80		C <sub>14</sub> H <sub>16</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>	320.29	106-107	52.41	5.11	8.71	52.50	5.03	8.74	
59	81		C <sub>13</sub> H <sub>13</sub> ClN <sub>2</sub> O	248.71	90-105 decom.	62.67	5.27	11.10	62.78	5.27	11.26	
60	82		C <sub>13</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub>	268.75	75-76.5	58.18	6.38	10.32	58.10	6.38	10.42	

Example No.	Compound No.	Structure	Formula	MWt	mp	C <sub>found</sub>	H <sub>found</sub>	N <sub>found</sub>	C <sub>exp</sub>	H <sub>exp</sub>	N <sub>exp</sub>	Note
61	83		C <sub>13</sub> H <sub>12</sub> ClFN <sub>2</sub> O	266.70	108.5-110	58.50	4.44	10.53	58.55	4.53	10.50	
62	84		C <sub>13</sub> H <sub>16</sub> ClFN <sub>2</sub> O <sub>2</sub>	286.74	79-80.5	54.61	5.77	9.69	54.46	5.62	9.77	
63	85		C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>	284.36	143-144	71.63	7.11	9.78	71.81	7.09	9.85	
64	86		C <sub>15</sub> H <sub>18</sub> F <sub>4</sub> N <sub>2</sub> O <sub>2</sub>	334.32	110-111.5	53.85	5.51	8.34	53.89	5.42	8.38	
65	87		C <sub>13</sub> H <sub>17</sub> FN <sub>2</sub> O <sub>2</sub>	252.29	90-93	62.09	6.70	10.78	61.89	6.79	11.10	
66	88		C <sub>14</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>2</sub>	282.77	114-115.5	59.52	6.88	9.62	59.47	6.77	9.91	
67	89		C <sub>10</sub> H <sub>11</sub> FN <sub>2</sub> O	194.21	205-208.5	61.74	5.70	14.21	61.85	5.71	14.42	
68	90		C <sub>14</sub> H <sub>18</sub> ClFN <sub>2</sub> O <sub>2</sub>	300.76	112.5-113.5	55.86	6.07	9.33	55.91	6.03	9.31	

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
69	91		C <sub>10</sub> H <sub>10</sub> ClFN <sub>2</sub> O	228.66	198-200.5							
70	92		C <sub>13</sub> H <sub>16</sub> ClFN <sub>2</sub> O <sub>2</sub>	286.74	81-82.5							
71	93		C <sub>13</sub> H <sub>17</sub> ClFN <sub>2</sub> O <sub>2</sub>	268.75	92.5-94	58.23	6.41	10.26	58.10	6.38	10.42	
72	94		C <sub>13</sub> H <sub>13</sub> FN <sub>2</sub> O	232.26	101.5-10.25	67.13	5.60	12.03	67.23	5.64	12.06	
73	95		C <sub>10</sub> H <sub>11</sub> ClN <sub>2</sub> O	210.66	oil							d
74	96		C <sub>14</sub> H <sub>19</sub> FN <sub>2</sub> O	250.32	100-102	67.10	7.64	11.05	67.18	7.65	11.19	
75	97		C <sub>14</sub> H <sub>19</sub> FN <sub>2</sub> O <sub>2</sub> (0.3 H <sub>2</sub> O)	266.32	77-79	61.83	7.30	10.39	61.74	7.28	10.29	
76	98		C <sub>16</sub> H <sub>21</sub> FN <sub>2</sub> O <sub>2</sub>	292.36	141-142.5	65.71	7.31	9.52	65.73	7.24	9.58	

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
77	99		C <sub>13</sub> H <sub>17</sub> FN <sub>2</sub> O <sub>2</sub>	252.29	118-120	61.59	6.89	10.95	61.89	6.79	11.10	
78	100		C <sub>13</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>3</sub>	284.75	90-92	54.93	6.07	9.79	54.84	6.02	9.83	
79	101		C <sub>14</sub> H <sub>20</sub> ClN <sub>3</sub> O.HCl	318.25	183-184	52.76	6.77	13.04	52.84	6.65	13.20	
80	102		C <sub>14</sub> H <sub>15</sub> F <sub>3</sub> N <sub>2</sub> O <sub>2</sub>	300.28	139.5-141	56.07	5.05	9.27	56.00	5.03	9.32	f
81	103		C <sub>14</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>2</sub>	282.77	oil							e
82	104		C <sub>14</sub> H <sub>16</sub> F <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	315.30	>150 decom.	53.05	5.18	13.24	53.33	5.11	13.32	g
83	105		C <sub>13</sub> H <sub>17</sub> FN <sub>2</sub> O <sub>2</sub>	252.29	77.5-79	61.82	6.83	11.05	61.89	6.79	11.10	
84	106		C <sub>15</sub> H <sub>19</sub> F <sub>3</sub> N <sub>2</sub> O <sub>2</sub>	316.33	123-124	57.03	6.08	8.88	56.96	6.05	8.85	



**Footnotes for Table 2:**

Footnote a: IR: 3373, 3316, 2923, 2855, 1639, 1620, 1557, 1488, 1462, 1434, 1378, 1304, 1153, 815  $\text{cm}^{-1}$ .

- 5 Footnote b: IR: 3500, 3429, 3346, 3274, 2925, 2854, 1614, 1556, 1466, 1420, 1407, 1052, 824, 536  $\text{cm}^{-1}$ .

Footnote c: IR: 3414, 3320, 3253, 2925, 2855, 1606, 1544, 1492, 1460, 1376, 1316, 1092, 822, 751, 705  $\text{cm}^{-1}$ .

- 10 Footnote d: IR: 3340, 3166, 2923, 2854, 1650, 1613, 1493, 1460, 1378, 1303, 1098, 820  $\text{cm}^{-1}$ .

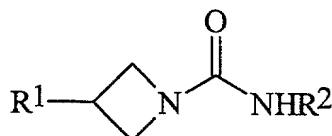
Footnote e: IR: 3310, 2964, 2878, 1632, 1538, 1494, 1482, 1462, 1398, 1328, 1093, 1015, 823, 529  $\text{cm}^{-1}$ .

Footnote f: compound (102) was made by the oxidation of compound (33), by methods known to those skilled in the art.

- 15 Footnote g: Compound (104) was made from compound (102) by methods known to those skilled in the art.

CLAIMS

1. A compound of formula (1)



5

(1)

wherein

R<sup>1</sup> is aryl; and

R<sup>2</sup> is hydrogen or alkyl;

and pharmaceutically acceptable addition compounds thereof.

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2. A compound according to claim 1 wherein R<sup>1</sup> is an aryl group selected from phenyl and naphthyl.

3. A compound according to claim 1 or 2 wherein R<sup>1</sup> has 1, 2 or 3 substituent groups.

15

4. A compound according to any preceding claim wherein R<sup>1</sup> is substituted with one or more substituent groups selected from halo, trifluoromethyl and tertiary-butyl.

5. A compound according to claim 4 wherein said halo groups are selected from chloro and fluoro.

20

6. A compound according to claim 1, 2, 3, 4 or 5 wherein R<sup>1</sup> is a meta- or para-substituted phenyl group.

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7. A compound according to claim 1 wherein R<sup>1</sup> is selected from 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl and 3-(trifluoromethyl)phenyl.

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8. A compound according to claim 1, 2, 3, 4 or 5 wherein  $R^1$  is selected from a 2,3-disubstituted phenyl group, a 2,4-disubstituted phenyl group, a 3,4-disubstituted phenyl group and a 3,5-disubstituted phenyl group.
- 5 9. A compound according to claim 8 wherein  $R^1$  is substituted by two halo groups, the same or different, or by one halo group and one trifluoromethyl group.
10. A compound according to claim 9 wherein  $R^1$  is dichloro-substituted, difluoro-substituted, chloro-fluoro-substituted or fluoro-trifluoromethyl-substituted.
- 10 11. A compound according to claim 1 wherein  $R^1$  is selected from 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-(trifluoromethyl)phenyl, 4-fluoro-3-(trifluoromethyl)phenyl and 3-chloro-5-fluorophenyl.
- 15 12. A compound according to any one of claims 1 to 11 wherein  $R^2$  is alkyl.
13. A compound according to any one of claims 1 to 12 wherein  $R^2$  is  $C_{1-8}$  alkyl.
14. A compound according to any one of claims 1 to 13 wherein  $R^2$  is alkenyl, alkynyl,  
20 hydroxyalkyl or alkoxyalkyl.
15. A compound according to any one of claims 1 to 13 wherein  $R^2$  is unsubstituted saturated cyclic or acyclic hydrocarbyl.
- 25 16. A compound according to any one of claims 1 to 13 wherein  $R^2$  is propyl, 2-propenyl, 2-propynyl or 2-hydroxypropyl.
17. A compound according to claim 1 wherein the compound is selected from 3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide, (*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-Fluorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide, (*R*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-Chlorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide, (*R*)-3-(4-Chlorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(4-Fluorophenyl)-*N*-(2-propenyl)azetidine-1-
- 30

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carboxamide, 3-(4-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide, (*R*)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, (*S*)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide, 3-(3-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide and 3-(4-(Trifluoromethyl)phenyl)-*N*-azetidine-1-carboxamide.

18. A compound according to any one of claims 1 to 17 for use in therapy.
19. Use of a compound according to any one of claims 1 to 17 in the manufacture of a medicament for the treatment (including prophylaxis) of CNS disorders.
20. Use according to claim 19 wherein said medicament is for the treatment (including prophylaxis) of anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness, alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse or spasticity.
21. Use according to claim 19 wherein said medicament is for the treatment (including prophylaxis) of anxiety or epilepsy.
22. Use of a compound according to any one of claims 1 to 17 in the manufacture of a medicament for muscle relaxation prior to surgery or surgical manipulation or as pre-medication prior to surgery.
23. A pharmaceutical composition comprising a compound according to any one of claims 1 to 17 in combination with a pharmaceutically acceptable carrier or excipient.
24. A method of treatment (including prophylaxis) of CNS disorders comprising administering to a patient in need of such treatment an effective dose of a compound according to any one of claims 1 to 17.
25. A method according to claim 24 wherein said method is for the treatment of anxiety, epilepsy, insomnia, including travel insomnia and insomnia associated with terminal illness,

alcohol withdrawal syndrome, chronic and acute pain, neurodegenerative diseases, symptoms relating to withdrawal from substance abuse or spasticity.

26. A method according to claim 24 wherein said method is for the treatment of anxiety  
5 or epilepsy.

27. A method of muscle relaxation prior to surgery or surgical manipulation or a method of pre-medication prior to surgery, comprising administering to a patient in need thereof an effective dose of a compound according to any one of claims 1 to 17.



**DECLARATION AND POWER OF ATTORNEY**

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

AZETIDINECARBOXAMIDE DERIVATIVES FOR TREATING CNS DISORDERS

(Attorney Docket No. 040283/0182)

the specification of which (check one)

       is attached hereto.

XX was filed on January 22, 1999 as United States Application Number or PCT International Application Number PCT/GB99/00223 and was amended on                                  (if applicable).

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified specification contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?
9801499.6	Great Britain	23 January 1998	Yes	
9824458.5	Great Britain	06 November 1998	Yes	

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date

I HEREBY CLAIM the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number

I HEREBY APPOINT the following registered attorneys and agents of the law firm of FOLEY & LARDNER to have full power to prosecute this application and any continuations, divisions, reissues, and reexaminations thereof, to receive the patent, and to transact all business in the United States Patent and Trademark Office connected therewith:

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I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

*David Reginald ADAMS*

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